Medical Staff Conference

Therapeutic Options in Treating Acute Myocardial Infarction

Discussant
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These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Acute myocardial infarction remains a devastating illness, but research over the past decade has shown that the initial and long-term outcome of coronary occlusion can be altered by immediate therapy. John Danforth, MD, will review the underlying rationale, the outcome, and his suggested guidelines for treatment in the hours after an acute myocardial infarction.*

JOHN W. DANFORTH, MD†: In the past 12 years we have witnessed unparalleled progress in treating the acute myocardial infarction patient. A number of promising therapeutic options were introduced, including thrombolytic therapy, emergent angioplasty, and immediate-intervention β-blockade therapy. For the first time, these interventions enabled physicians to substantially influence the pathophysiology of this disorder. As the benefits of immediate-intervention therapy became evident, the philosophy of treating an acute myocardial infarction changed dramatically—from expectant observation to relatively aggressive intervention.

Now the medical community is attempting to tackle the controversies that have evolved in the wake of this recent departure from convention. At present, the rationale for immediate-intervention therapy is well accepted. Considerable uncertainty persists, however, regarding the relative merits of the various therapeutic options that have become available. Although a definitive resolution of these issues must await the completion of several ongoing trials, there are enough data to draw preliminary conclusions about the value of some of these interventions. I will review these conclusions and apply them to the development of a preliminary treatment strategy for patients with acute myocardial infarction.

Thrombolytic Therapy

There is little debate that thrombolytic therapy is the cornerstone of treatment for an acute myocardial infarction. The timely administration of thrombolytic therapy consistently has been shown to reduce both infarct size and postinfarction mortality.[1] Although thrombolytic therapy is now considered the standard of care in treating an acute myocardial infarction, there is little consensus on the agent of choice. To understand the issues that have contributed to this uncertainty requires an appreciation of the limitations of thrombolytic therapy in general.

We now recognize that thrombolytic therapy at best permits the salvage of a modest fraction of the myocardium in the region at risk for infarction. This circumstance derives from several facts:

- Myocardial necrosis occurs rapidly with sustained oxygen deprivation;
- Patients frequently seek medical attention late in the course of an infarction; and
- Necrosis probably continues unabated for 30 to 60 minutes following the intravenous administration of a thrombolytic agent.

Although unknown, current speculation maintains that an acute myocardial infarction becomes complete in humans within 4 to 12 hours (mean, 6 hours) following the onset of symptoms. This variation among patients probably reflects the effects of many factors, including heart rate, afterload, and collateral blood flow, on the rate of necrosis development. These presumptions have been extrapolated from the results of studies in animals. An acute infarction is completed within two hours in pigs[2] and within six hours in dogs.[3] Because the extent of native collateral development in humans is intermediate between that of pigs and dogs, it is reasonable to presume that the time to completion of an acute infarction among patients with limited secondary collateral development varies between two and six hours. This probably underestimates the time course of most acute infarctions, however, because many patients have evolved secondary collaterals within the infarct zone. Taken together, these observations suggest that the time course for an acute infarction varies from 4 to 12 hours in patients who survive the initial event.

The rapidity with which necrosis develops following an acute myocardial infarction stems from the poor development of the hexose monophosphate shunt within the heart and the heart's relatively high oxygen extraction ratio.[4] The heart

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ABBREVIATIONS USED IN TEXT

GISSI II = Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico [trial], phase II
ISIS-2 = Second International Study of Infarct Survival
rt-PA = recombinant tissue plasminogen activator
TAMI = Thrombolysis Angioplasty in Myocardial Infarction [study group]
TIMI I and II = Thrombolysis in Myocardial Infarction [trial], phases I and II
UCSF = University of California, San Francisco

is incapable of sustained anaerobic metabolism and cannot respond to an ischemic insult by recovering more oxygen from a limited blood supply.[4] In short, the heart cannot tolerate sustained oxygen deprivation, and necrosis develops rapidly in this circumstance.

Given the rapidity with which necrosis develops within the infarct zone and the propensity of patients to seek medical attention relatively late in the course of an acute myocardial infarction, it is reasonable to presume that extensive necrosis has already occurred in most patients by the time thrombolytic therapy can be administered (Figure 1), and necrosis probably continues for a limited time even after thrombolytic therapy is given. With respect to this latter issue, it develops that thrombolysis is a time-dependent process. According to the results of phase I of the Thrombolysis in Myocardial Infarction (TIMI I) trial,[5] for example, recannalization commonly develops 30 to 90 minutes following the intravenous administration of thrombolytic therapy (Figure 2). These facts suggest that for most patients the myocardial salvage potential of thrombolytic therapy is limited.

It is precisely this situation that has hampered efforts to compare the clinical usefulness of the various thrombolytic agents that have become available. For example, we now recognize that the thrombolytic efficacy of recombinant tissue plasminogen activator (rt-PA) is probably superior to that of streptokinase.[5-12] To date, two studies have been published comparing the relative efficacy of these agents: the TIMI I trial[5] and the European Cooperative Study.[6] The data favor the use of rt-PA versus streptokinase (Figure 3). In addition, the acute recannalization data derived from virtually all the single-drug, placebo-controlled trials reported to date indicate that rt-PA is superior to streptokinase from the standpoint of the initial thrombolytic efficacy (Figure 3).[7-12]

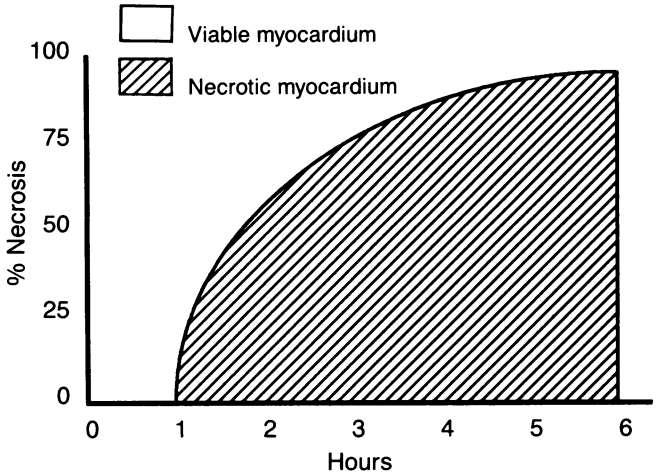

Figure 1.—A hypothetical myocardial necrosis curve is shown, indicating the portion of the infarct zone that sustains irreversible damage in the hours after coronary occlusion.

Despite the higher early recannalization rates reported following the administration of rt-PA versus streptokinase, it has not been proved that rt-PA has a higher potential for preserving myocardium. For example, the timely administration of both agents appears to confer a similar effect on the left ventricular ejection fraction (Table 1).[7,9,10,13-19] The TIMI I trial is perhaps the best example of this disparity.[5] This study was designed to compare the thrombolytic and myocardial salvage potential of intravenous rt-PA versus intravenous streptokinase. The results indicated that the thrombolytic rate for rt-PA was twice the corresponding rate for streptokinase: 62% versus 31%. Yet the data suggested that the myocardial salvage potential of the two agents was similar.[18]

In retrospect, it seems likely that the relatively prolonged delay to therapy in this study (mean, 5.3 hours) accounts for this disparity. If one assumes that an infarct becomes com-

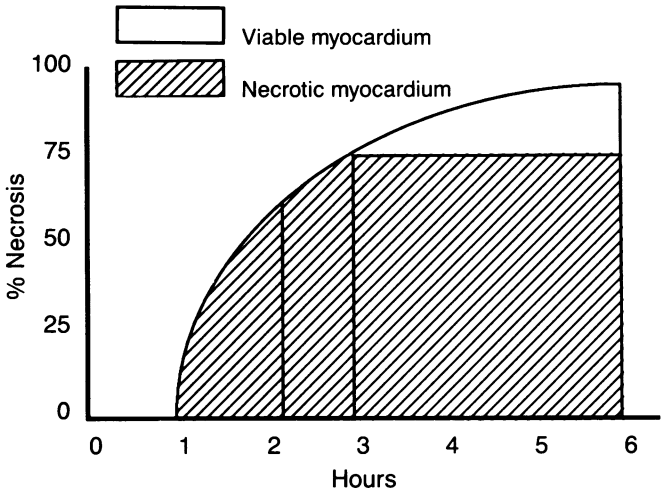

Figure 2.—The graph shows the myocardial salvage potential of thrombolytic therapy administered two hours after coronary occlusion. Thrombolysis occurs 30 to 90 minutes after drug administration, and necrosis probably continues until recannalization is achieved.

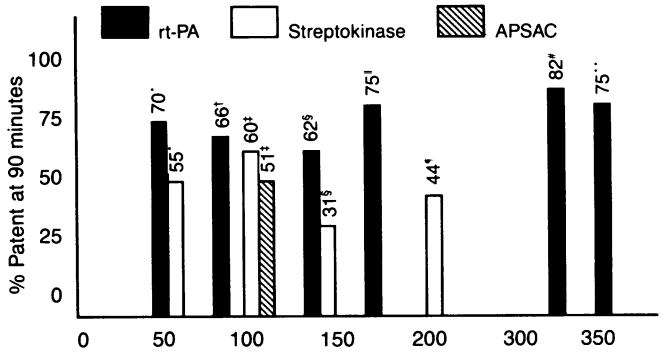

Figure 3.—Recannalization rates following intravenous thrombolytic therapy were determined by coronary arteriography that was done within 90 minutes. The studies are presented in order of size and are identified by footnote symbols. The juxtaposition of bars indicates that two agents were administered on a randomized basis in the same trial.

APSAC = anisoylated plasminogen streptokinase activator complex, rt-PA = recombinant tissue plasminogen activator
*From Verstraete et al[6]; rt-PA: 64 patients, streptokinase: 65 patients.
†From Guerci et al[9]; 72 patients.
‡From the APSAC trial[12]; streptokinase: 111 patients, APSAC: 115 patients.
§From the TIMI I trial[5]; rt-PA: 143 patients; streptokinase: 147 patients.
¶From the TIMI IIA Research Group[10]; 192 patients.
#From Stack et al[11]; 216 patients.
**From the TIMI II pilot study[8]; 317 patients.
**From the TAMI study group[7]; 386 patients.

TABLE 1.—*Effect of Immediate-Intervention Angioplasty on In-hospital Mortality*

Trial	Patients, No.	Immediate Angioplasty, %	Deferred Angioplasty, %
TAMI, 1987[7]	197	4	1
European Cooperative, 1988[19]	367	7	3
TIMI IIA, 1988[10]	389	8	5

TAMI=Thrombolysis Angioplasty in Myocardial Infarction study group, TIMI IIA=Thrombolysis in Myocardial Infarction trial, phase IIA

plete within six hours after the start of symptoms and that an hour is required to achieve thrombolysis following the administration of therapy,[5] then it is reasonable to assume most patients enrolled in the TIMI I trial probably had a completed infarction before thrombolysis was accomplished. In this circumstance, one would not expect recannalization to influence the extent of necrosis.

Although the TIMI I trial was an exceptionally late-entry trial, it is likely that the previous considerations probably apply to the interpretation of much of the data generated on the clinical use of thrombolytic therapy. Taken together, the current data indicate that rt-PA is a superior thrombolytic agent relative to streptokinase, and yet both agents appear to have the same effect on the global left ventricular ejection fraction.[5-17] Although the imprecision of left ventriculography may partially account for this disparity, it is still reasonable to presume that most of the myocardium within an infarct zone had probably sustained irreversible damage before thrombolysis could be achieved in most patients in these trials and that this circumstance limits the potential difference between these two agents in preserving myocardium.

Every effort must be made to deliver these agents as early as possible during the course of an infarction. Investigators for the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) trial reported that the possible effect of the use of streptokinase on postinfarction mortality was inversely related to the time delay to therapy.[20] According to the results of this trial, administering streptokinase within an hour following the start of symptoms was associated with a 46% reduction in postinfarction mortality ($P<.0001$), whereas administering this agent five hours thereafter did not significantly influence mortality.[20] Topol and colleagues showed that the myocardial salvage potential of thrombolytic therapy is similarly dependent on the time delay to therapy.[21] These investigators reported that the mean left ventricular ejection fraction of patients treated with rt-PA a mean of 3.9 hours after the onset of symptoms was substantially lower ($51\% \pm 10\%$) than the corresponding ejection fraction of persons who received therapy within 2 hours after the start of symptoms ($56\% \pm 9\%$).[21]

Despite the obvious implications of these data, it is clear that an enormous effort will be required to speed the delivery of therapy for acute myocardial infarction. We will need to develop large-scale educational programs that will encourage patients to seek medical attention during the early phase of an infarction. Diagnostic tools for the rapid detection of an acute infarction will have to be refined. Steps will need to be taken in hospitals to minimize the delay before therapy is given to patients who present with an acute infarction. Programs probably will need to be developed for the administration of thrombolytic agents in the field in rural communities with prolonged ambulance "scoop and carry" times.

It appears that thrombolytic therapy confers about a 10% to 20% reduction in infarct size[22] and a 2% to 3% reduction in postinfarction mortality. The second figure is based on a mean six-week postinfarction mortality rate for 10% to 12% of patients who survive long enough to receive medical attention and a relative 20% to 30% reduction in mortality following the administration of single-drug thrombolytic therapy. Virtually all mortality data are now reported in terms of a percent of a percent, and this convention can be misleading.

Adjuvant Therapy

Angioplasty

Given the limitations of thrombolytic therapy, considerable effort has been directed toward developing interventions that can be administered in conjunction with thrombolytic therapy to further contain the formidable morbidity and mortality of an acute infarction. Of the various interventions proposed, emergent angioplasty was originally considered one of the most promising. It was thought that this procedure might limit the development of necrosis regardless of a patient's response to thrombolytic therapy. Among those who did not respond—in whom recannalization failed to occur, for example—it was hoped that angioplasty might permit the salvage of viable myocardium within the region at risk for necrosis.[23] Among those who did respond, it was hoped that angioplasty might offset the continued necrosis that probably occurs for a brief time following recannalization.

An imbalance between the myocardial oxygen supply and the demand probably persists for hours to days among the majority of patients who respond favorably to thrombolytic therapy. The myocardial oxygen demand remains substantially increased because sympathetic stimulation of the heart continues for several days after an infarction.[24] Similarly, the supply of myocardial oxygen probably remains depressed in the region at risk because blood flow within the infarct-related vessel is probably compromised by the presence of residual thrombous formation that may persist for days to weeks following recannalization.

Although there is little direct evidence to confirm the presumption that intracoronary thrombi commonly persist following recannalization, it is intriguing to note that the severity of infarct-related lesions identified immediately following recannalization tends to decrease over time.[7,19] Given the improbability that atheromas can undergo spontaneous autolysis, it is likely that this phenomenon reflects thrombolysis of clot superimposed on the infarct-related lesion. We now recognize that, among unstable angina patients, thrombus accumulation occurs commonly in the vicinity of an intracoronary plaque and that this thrombus is angiographically indistinguishable from underlying atheroma.[25] The presence of this thrombus commonly contributes to the apparent severity of stenotic lesions considered responsible for the development of ischemia among these patients.[24] In retrospect, it is likely that the presence of superimposed clot formation accounts for the observation that the severity of infarct-related lesions tends to diminish with time.[26,27] It is reasonable to assume that this thrombus impairs blood flow and compromises oxygen supply to the region at risk for infarction.

Myocardial oxygen demand probably remains high and

the supply low for hours to days following an acute event among most patients who respond favorably to thrombolytic therapy. As a result, it seems likely that myocardial ischemia and possibly necrosis continue for a limited period following recannalization. We may speculate that doing an emergent angioplasty might offset this imbalance and permit the further containment of an acute infarction. There is some evidence from studies of animals to suggest that ablation of an infarct-related lesion reduces infarct size relative to recannalization alone.[28]

The clinical experience with immediate angioplasty, however, has been discouraging. The mortality rates for every randomized trial reported to date have been consistently higher among patients receiving immediate angioplasty (Table 1).[7,19,29] The results of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trial[7] and the European Cooperative trial[19] indicated that immediate angioplasty increased the risk for reocclusion among patients who had responded favorably to thrombolytic therapy. The results of the TAMI trial further indicated that among patients who had not responded to thrombolytic therapy, salvage angioplasty did not influence the infarct size.[23] More recently, the results of phase II of the Thrombolysis in Myocardial Infarction (TIMI II) trial indicated that performing an angioplasty three days after an infarction provided no benefit relative to conservative therapy in reducing postinfarction morbidity and mortality.[30] Among patients presenting with shock, however, immediate angioplasty has been shown to reduce postinfarction mortality.

At present, there is no consensus on the role of immediate angioplasty in the treatment of an acute infarction. The results have been mixed, and considerable data suggest that this procedure is counterproductive in the setting of an acute infarction. Although the role of emergent angioplasty in treating an acute myocardial infarction remains to be determined, it is probably reasonable to conclude at this juncture that the benefit of this procedure is less than what was anticipated. Given our current uncertainty, this procedure probably should be reserved for patients enrolled in rigidly controlled trials; doing this procedure on a routine basis is not warranted. Considerable pathophysiologic evidence suggests that angioplasty may even be counterproductive. We now suspect that infarction is often precipitated by the rupture of an atheromatous plaque.[31] This process appears to cause the release of procoagulant factors into the systemic circulation, which presumably enhances the thrombolytic potential of the ruptured endothelial surface.[32,33] The interaction between a thrombogenic circulation and the prothrombotic endothelial surface presumably culminates in the development of an intravascular thrombus.

If this mechanism does account for acute infarction, then it is entirely conceivable that an angioplasty carried out during the early phase of an acute myocardial infarction might aggravate this condition. Balloon-mediated angioplasty is accomplished by creating multiple microscopic dissections within the atheromatous lesion subjected to mechanical dilatation. Most of these dissections are small—well below the power of resolution of conventional angiography. As a result, they often evolve without detection. While they are well tolerated under normal circumstances, it is conceivable that the creation of these microdissections during a phase of enhanced coagulation might predispose a patient to rethrombosis and hence reocclusion. In several trials of emergent angioplasty, reocclusion occurred with such frequency in patients who have responded favorably to thrombolytic therapy that the investigators have recommended withholding emergent percutaneous transluminal coronary angioplasty from these patients.[7,19]

Although immediate angioplasty cannot be recommended at this juncture, it is intriguing to speculate that the development of more effective platelet inhibitors might unmask benefits of the procedure in the initial treatment period. Several promising agents are currently undergoing preclinical trials,[34,35] and the introduction of these agents may revitalize the original enthusiasm for this promising procedure.

Aspirin

Given the current consensus regarding the pathogenesis of an acute myocardial infarction, aspirin should offer effective therapy (Figure 4). The results of the Second International Study of Infarct Survival (ISIS-2) trial indicate that administering aspirin alone is associated with a 22% reduction in postinfarction mortality.[36] The results of this and other trials indicate that aspirin also enhances the therapeutic potential of both rt-PA and streptokinase (Figures 5 and 6). For these reasons, aspirin therapy is strongly recommended.

β-Blockers

The results of the TIMI II trial strongly favor the administration of β-blockers in conjunction with thrombolytic therapy during the acute phase of an infarction.[30] They showed that conventional doses of intravenous or oral metoprolol tartrate given during the early phase of an acute infarction resulted in a 27% reduction in the incidence of postinfarction ischemia compared with giving aspirin and rt-PA alone, and that intervention with this agent within two hours after the start of symptoms resulted in a 58% reduction in morbidity and mortality at six weeks after an infarction compared with giving aspirin and rt-PA alone.

In retrospect, it seems logical that thrombolytic and β-blockade therapy should be synergistic in treating an acute infarction. Thrombolytic agents enhance the myocardial ox-

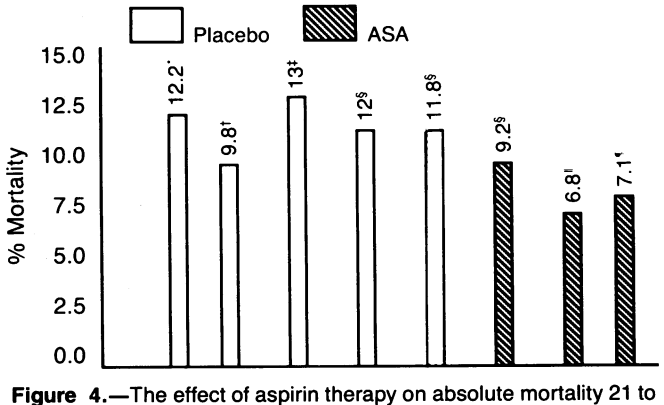

Figure 4.—The effect of aspirin therapy on absolute mortality 21 to 30 days after a myocardial infarction is shown in control groups. Mortality rates among the control groups of major placebo-controlled trials of thrombolytic therapy are indicated by the open bars. The hatched bars refer to studies in which the control groups received aspirin.

*From the AIMS Trial[38]; 502 patients.
†From Wilcox et al[39]; 2,490 patients.
‡From Gruppo Italiano[20]; 5,852 patients.
§From the ISIS-2 trial[36]; placebo: 8,595 patients, 8,600 patients; aspirin: 8,592 patients.
‖From the European Cooperative Study Group[22]; 366 patients.
¶From the ISAM Study Group[40]; 463 patients.

ygen supply, and β-blocking agents reduce the myocardial oxygen demand. Given that thrombolysis is a time-dependent process,[5] the early administration of β-blocking agents probably delays the onset of necrosis and thus enhances the salvage potential of thrombolytic therapy (Figure 6). Studies have shown that the rate of development of necrosis within the myocardium of animals varies in response to changes in the heart rate.[42] Specifically, necrosis develops more slowly in animals with lower heart rates.[42] The effectiveness of adjuvant β-blockade therapy, therefore, will probably depend on the heart rate or the cross product of a patient, or both. Patients presenting with tachycardia should derive the greatest benefit from β-blockade therapy and should be treated aggressively. Conversely, it is unlikely that administering β-blocking agents will confer significant benefit in persons with a relatively low cross product.

Nitrates

In theory, the use of nitrates should enhance the myocardial salvage potential of thrombolytic agents. Administering nitrates has been shown to enhance collateral blood flow in the regions subserved by an occluded vessel in both humans[43] and animals,[44] and it is reasonable to presume that collateral blood flow delays the onset of necrosis within the potential infarct zone. In this regard, the results of the TIMI I trial, a particularly late-entry trial, showed that myocardial preservation with thrombolytic therapy occurred only in patients with angiographic evidence of collaterals.[5] In retrospect, these results suggest that the presence of collaterals extended the window of opportunity for thrombolytic therapy, and this conclusion, in turn, supports the hypothesis that collateral blood flow delays the onset of necrosis. If so, and if nitrates enhance the amount of collateral flow within the region at risk, then they should be synergistic with thrombolytic agents in preserving the myocardium. There are no clinical data to support this contention, however. Of interest is that in a 1988 study, nitrates were found to significantly reduce postinfarction mortality.[45]

Calcium Channel Blockers

At present, calcium channel blockers have little or no role in managing the acute phase of a myocardial infarction.[46] Administering nifedipine has been shown to enhance mortality,[47] infarct size,[48] and reinfarction rate.[48] The adverse effect of nifedipine presumably stems from its propensity to provoke a reflex tachycardia. The administration of diltiazem hydrochloride during the postinfarction period is well tolerated but has not been shown to reduce mortality when administered routinely to patients after an infarction.[49] Conversely, one trial has shown that administering diltiazem reduces the risk of progression from a non-Q wave to a Q wave infarction.[50] However, the agent was given 24 hours after hospital admission. The role of diltiazem in the treatment of the acute phase—that is, the first 6 to 12 hours—of an infarction is unclear, and it should not be administered in lieu of nitrates or β-blocking agents until data are presented to the contrary. Diltiazem, like nifedipine, lowers blood pressure and thus might preclude the administration of β-blockers or nitrates, which appear more effective in this circumstance.

Lidocaine

The results of a 1988 analysis[51] indicate that the administration of lidocaine is associated with an increased risk of death after a myocardial infarction. Although the subject of considerable controversy, it is probably reasonable to conclude that lidocaine prophylaxis should not be administered routinely to the postinfarction patient.

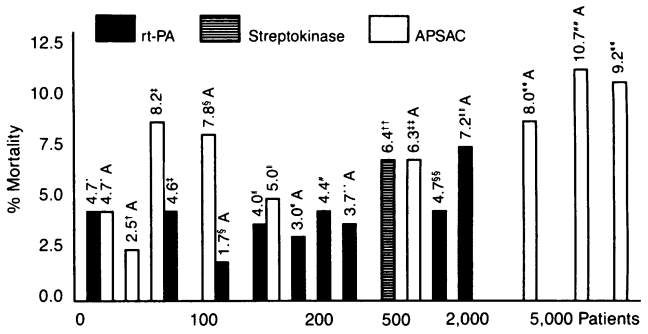

Figure 5.—Mortality rates are shown for the treatment groups of major trials of thrombolytic therapy 21 to 30 days after myocardial infarction. Studies are presented in order of size. The letter *A* indicates that aspirin was administered in conjunction with thrombolytic therapy.

APSAC = anisoylated plasminogen streptokinase activator complex, rt-PA = recombinant tissue plasminogen activator
*From Verstraete et al[6]; rt-PA: 64 patients, streptokinase: 65 patients.
†From White et al[15]; 79 patients.
‡From the Plasminogen Activator Italian Multicenter Study Group[41]; streptokinase: 85 patients, rt-PA: 86 patients.
§From White et al[17]; streptokinase: 110 patients, rt-PA: 115 patients.
‖From TIMI, phase I[5]; rt-PA: 143 patients; streptokinase: 147 patients.
¶From the European Cooperative Study Group[19]; 184 patients.
#From TIMI, phase II[8]; 317 patients.
**From the European Cooperative Study Group[22]; 355 patients.
††From the AIMS Trial Study Group[38]; 502 patients.
‡‡From the ISAM Study Group[40]; 859 patients.
§§From the TIMI II Study Group[30]; 1,626 patients.
‖‖From the Anglo-Scandinavian Study of Early Thrombolysis[39]; 2,516 patients.
¶¶From the ISIS-2 Collaborative Group[36]; with aspirin: 4,292 patients, without aspirin: 8,592 patients.
##From Gruppo Italiano[20]; 5,860 patients.

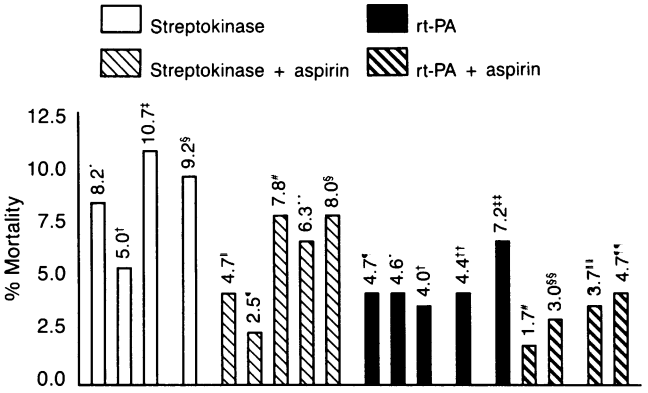

Figure 6.—Effect of aspirin therapy on postinfarction (21 to 30 days) mortality is shown for patients receiving thrombolytic therapy. The data contained in Figure 5 are here regrouped according to treatment regimen and are presented in order of increasing size of the study group.

rt-PA = recombinant tissue plasminogen activator
*From the Plasminogen Activator Italian Multicenter Study Group[41]; streptokinase: 85 patients, rt-PA: 143 patients.
†From TIMI, phase I[5]; streptokinase: 147 patients, rt-PA: 143 patients.
‡From Gruppo Italiano[20]; 5,860 patients.
§From the ISIS-2 Collaborative Group[36]; streptokinase: 8,592 patients, streptokinase plus aspirin: 4,292 patients.
‖From Verstraete et al[6]; streptokinase plus aspirin: 65 patients, rt-PA: 64 patients.
¶From White et al[15]; 79 patients.
#From White et al[17]; streptokinase plus aspirin: 110 patients, rt-PA plus aspirin: 115 patients.
**From the ISAM Study Group[40]; 859 patients.
††From TIMI, phase II[8]; 317 patients.
‡‡From the Anglo-Scandinavian Study of Early Thrombolysis[39]; 2,516 patients.
§§From the European Cooperative Study Group[19]; 184 patients.
‖‖From the European Cooperative Study Group[22]; 355 patients.
¶¶From the TIMI II Study Group[30]; 1,626 patients.

TABLE 2.—*Effect of Thrombolytic Therapy on the Global Left Ventricular Ejection Fraction After Myocardial Infarction*

Trial	Agent Administered	Time Delay to Therapy, hours	Patients, No. Treatment/ Control	Method Used to Determine Ejection Fraction	Ejection Fraction			P Value	Date of Assessment, weeks
					Treatment	Control	Δ		
Western Washington, 1988[13] ...	Streptokinase	<6	191/177	RVG	50.7	47.0	3.7	.08	8
White et al (Auckland), 1987[15] ..	Streptokinase	<4	79/93	Angiography	59.0	53.0	6.0	<.005	3
White et al, 1989[17]	Streptokinase	<3	135	Angiography	58.0	...	...	...	3
White et al, 1989[17]	rt-PA	<3	135	Angiography	58.0	...	...	...	3
Johns Hopkins, 1987[9]	rt-PA	<4	72/66	RVG	53.2	46.4	6.8	<.02	1½
O'Rourke et al, 1988[14]	rt-PA	<2.5	74/71	RVG	52.0	48.0	4.0	.08	3
O'Rourke et al, 1988[14]	rt-PA	<2.5	74/71	Angiography	61.0	54.0	7.0	<.006	3
Australian, 1988[16]	rt-PA	<4	73/71	Angiography	57.7	51.7	6.0	.04	1

rt-PA=recombinant tissue plasminogen activator, RVG=radionuclide ventriculography

The Use of Streptokinase and Recombinant Tissue Plasminogen Activator

Several misunderstandings have contributed to the perpetuation of the controversy concerning the relative merits of using rt-PA versus streptokinase. Originally, both agents were proposed to be equally effective in restoring blood flow during the first 1 to 2 hours following the occurrence of symptoms.[52] This impression was based on an extrapolation of the data generated during the course of the TIMI I trial,[5] however, and there is virtually no evidence to substantiate this conjecture. During the course of this trial, only four patients received either agent within two hours after the onset of chest pain. Among the 28 patients who received thrombolytic therapy within three hours following the onset of chest pain, the recannalization rates for patients given rt-PA and streptokinase were 80% and 44%, respectively.[53] Although there are no reliable data that can be used to compare the thrombolytic potentials of using rt-PA or streptokinase among persons who seek medical attention within two hours of having chest pain, the data generated during both comparative trials and placebo-controlled studies consistently indicate that rt-PA therapy is superior to that of streptokinase in thrombolytic efficacy. Pending any data to the contrary, it is probably inappropriate to assume that the two agents have similar thrombolytic potential when administered within two hours after the start of symptoms.

It has recently been suggested that using streptokinase in combination with aspirin is equivalent to using rt-PA. This conjecture is derived from an interpretation of the ISIS-2 trial[36] mortality data and warrants review. The ISIS-2 trial was a large, multicenter, randomized, placebo-controlled study designed to compare the effects of aspirin, streptokinase, and combined aspirin plus streptokinase therapy on postinfarction mortality. The results indicated that administering aspirin and streptokinase resulted in a 43% reduction in mortality compared with placebo. This was considered comparable to the 46% reduction in mortality reported in the European Cooperative trial,[19] a placebo-controlled rt-PA mortality trial. Because administering aspirin has been shown to confer a profound effect on mortality,[36] this comparison does not provide any useful information concerning the relative efficacy of rt-PA versus streptokinase. Inspection of the data derived from both the ISIS-2 trial and the European Cooperative trial indicates that treatment with rt-PA versus streptokinase resulted in a 46% versus 23% reduction in mortality among comparable treatment and control groups that took aspirin. In short, the data collected to date, including the data from the ISIS-2 trial, have consistently favored the use of rt-PA over streptokinase in reducing postinfarction mortality. Furthermore, it appears that the use of aspirin also enhances the effectiveness of rt-PA (Figure 6).

A third area of confusion concerns the effect of these two agents on the ejection fraction. In general, administering thrombolytic agents results in a modest improvement in the global left ventricular ejection fraction (Table 2). The limited effects of thrombolytic therapy in this regard probably stem from the fact that considerable necrosis commonly develops before recannalization is achieved. In retrospect, it appears that both agents have a similar effect on the ejection fraction (Table 2); however, a recent re-evaluation of the wall motion findings from the TIMI I trial indicated that the regional wall motion was better following the administration of rt-PA versus streptokinase therapy, despite the similarity of the global ejection fractions for both groups of patients.[54] Furthermore, the similarity in global ejection fractions should not be misconstrued to suggest that the two agents are equally useful, as mortality rates have been consistently lower after the administration of rt-PA. One interpretation of these observations is that the prognosis following an acute infarction tends to correlate with coronary patency and not with the ejection fraction.[37]

While rt-PA is consistently more expensive, it is superior to streptokinase in reducing postinfarction mortality. Both agents appear to have a similar effect on the left ventricular ejection fraction and a similar rate of bleeding complications. Given these findings, the controversy surrounding the use of rt-PA versus that of streptokinase can be reduced to a relatively straightforward question: How much will it cost to treat patients with rt-PA versus streptokinase? The data are currently insufficient to answer this question. It is hoped, however, that the results of the GISSI II trial will prove helpful in this regard. This is an ongoing, multicenter trial designed to determine the effects of both rt-PA and streptokinase on postinfarction mortality. The results should be reported in early 1990.

If the results of this trial indicate that the difference in absolute mortality between the rt-PA and streptokinase treatment groups is relatively small, then various other social and financial issues will need to be considered—including the propensity of patients to require additional procedures following the administration of these agents, the frequency with which recipients of these agents return to work, their corresponding productivity, and so forth—to determine the relative cost-effectiveness of the two agents. Of interest is the conclusion from a study in Canada that the use of rt-PA is more cost-effective than that of streptokinase when these

issues are included in determining the relative expense of the two agents.[55]

Although the GISSI II trial will provide some critical data that can be used to determine the relative cost-effectiveness of these two agents, it is likely that a number of economic, social, and ethical issues will need to be considered in order to resolve the controversy that has evolved concerning the relative merits of rt-PA versus streptokinase. Many of these issues are relatively imponderable, and hence it is conceivable that this controversy will continue long after the publication of this trial.

Summary

The management of an acute infarction has changed dramatically over the past 12 years. Although progress has been made, considerable controversy persists. Definitive conclusions must await the completion of ongoing and future trials. There are enough data, however, to permit several conclusions:

- Thrombolytic therapy constitutes the cornerstone of treatment of an acute infarction.
- The efficacy of thrombolytic therapy is critically dependent on the time delay to therapy.
- In recannalizing thrombosed vessels and in reducing mortality, rt-PA is superior to streptokinase. Both agents are similar in terms of impact on the ejection fraction and the incidence of bleeding complications.
- The controversy between rt-PA and streptokinase therapy concerns cost-effectiveness more than biologic efficacy.

Administering a thrombolytic agent alone confers only a modest reduction in postinfarction mortality and infarct size. Hence, these agents should be given in conjunction with adjuvant therapy. Aspirin, β-blockers, and nitrates are among the most promising agents for adjuvant therapy. The data currently do not support doing a routine angioplasty in patients with acute infarction. It is entirely conceivable, however, that data will evolve in support of this approach following the introduction of devices or agents, or both, that effectively prevent the development of reocclusion of the vessel supplying the area of infarction.

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